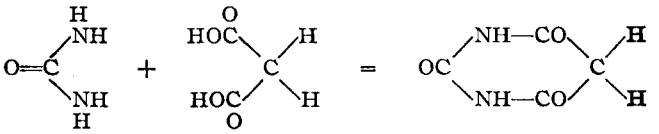
Barbiturates: A Blessing and a Menace*

By SAMUEL W. GOLDSTEIN†,‡

The development and therapeutic status of barbituric acid derivatives are reviewed and those in general use as therapeutic agents are tabulated. Data are presented on the incidence of poisonings in the United States by barbiturates. The nature of problems relating to the use and misuse of barbiturates is discussed and the need for corrective uniform state legislation is stressed.

DURING the past forty-two years there have been five outstanding discoveries which have greatly fortified the armamentarium of the physician: (*a*) barbiturates (1903); (*b*) salvarsan (1907); (*c*) insulin (1922); (*d*) sulfonamides (1935), first prepared in 1909; (*e*) antibiotics (1940), although penicillin was first discovered in 1929. No group of drugs caused such chemical activity as the barbiturates until the advent of the sulfonamides.

Here was a combination of urea, the first organic compound to have been prepared synthetically, and malonic acid, a classic example of organic synthesis, to form malonylurea or barbituric acid.



Urea Malonic acid Malonylurea (barbituric acid)

The two hydrogen atoms in the methylene group of barbituric acid are very reactive and can be replaced indirectly by one or two aliphatic or aromatic groups to form compounds having hypnotic properties.

The first of these compounds to be introduced into medicine was the diethyl substituted product, barbital, prepared in 1903 by Emil Fischer and von Mering (1) and patented under the name veronal. This was followed by phenobarbital or luminal which differs from barbital in that one of the ethyl groups is replaced by a phenyl group. The barbituric acid derivatives are only sparingly soluble in water, but the sodium salts, in which sodium replaces a hydrogen atom attached to nitrogen, are freely soluble in water and are referred to as the "sodium barbiturate," the "soluble barbiturate," or the "barbiturate sodium." Starting with thiourea in place of urea a new series of barbiturates has been prepared, the best of which is sodium ethyl (1-methylbutyl) thiobarbiturate or pentothal sodium.

APPROVED BARBITURATES

Over 1500 different barbituric acid derivatives have been prepared, but less than twenty have survived clinical use. Table I lists the clinically useful barbiturates that are recognized in the United States Pharmacopœia XII and New and Nonofficial Remedies 1946, and gives the trade names, synonyms, and chemical names, the approximate relative duration of action, and the average adult hypnotic dose. Barbital was the first of the malonylurea series of drugs to become official in the U. S. P. and is still considered to be one of the best hypnotics. For years the drug manufacturers introduced barbiturates under confusing trade names, each claiming superior virtues for his product with respect to its potency, efficiency or shortness of action, margin of safety, and form and size or color of tablet or capsule. Gardner (2) considers only five barbiturates as essential: Barbital and phenobarbital and their sodium derivatives; pentobarbital sodium; evipal sodium, for intravenous anesthesia; and pentothal sodium, for prolonged intravenous anesthesia. Evipal and pentothal are recognized by the American Medical Association in New and Nonofficial Remedies, while the first three are recognized

* Received Nov. 27, 1946, from the State of Maryland Department of Health, Baltimore.

† Pharmaceutical Chemist, State of Maryland Department of Health.

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in the U. S. P. XII. Pentothal sodium, under the name thiopental sodium, will be included in the U. S. P. XIII which will become official in 1947. Gardner suggests that physicians should limit their barbiturate prescriptions to these five and thereby relieve the pharmacists of the necessity of stocking a large number of named and unnecessary preparations.

are useful in psychic sedation, producing a sound sleep the night before a surgical operation, and for allaying fears just before the operation. The average dose used to produce sleep does not depress the respiration, but large doses can cause death by respiratory failure. Overdoses of barbiturates can indirectly diminish the secretion of urine, and since urine is the most important avenue

TABLE I.—BARBITURATES ACCEPTED FOR CLINICAL USE

Trade Names, Synonyms, and Chemical Names	Recognized in	Duration of Action (Approx.)[a]	Average Adult Hypnotic Dose in Gm.
Alurate[b] Allylisopropylbarbituric acid	N. N. R.	M	0.065–0.13
Amytal[b] Isoamylethylbarbituric acid	N. N. R.	M	0.1–0.3
Barbital[b,c], Barbitone, Veronal Diethylbarbituric acid	U. S. P.	P	0.3
Dial Diallylbarbituric acid	N. N. R.	P	0.1–0.3
Hexobarbital Soluble, Evipal Sodium, Evipal Soluble Sodium N-methylcyclohexenylmethylbarbiturate	N. N. R.	VS	.....
Ipral Calcium,[b] Probarbital Calcium Calcium ethylisopropylbarbiturate	N. N. R.	P	0.12–0.25
Neonal, Soneryl, Butobarbital *n*-Butylethylbarbituric acid	N. N. R.	P	0.05–0.1
Nostal Isopropyl-β-bromallylbarbituric acid	N. N. R.	P	0.1–0.3
Ortal Sodium Sodium *n*-hexylethylbarbiturate	N. N. R.	M	0.2–0.4
Pentobarbital Sodium, Nembutal Sodium ethyl(1-methylbutyl)barbiturate	U. S. P.	M	0.1
Pentothal Sodium, Thiopental Sodium[d] Sodium ethyl(1-methylbutyl)thiobarbiturate	N. N. R.[e]	VS	.....
Pernoston[b] *sec.*Butyl-β-bromallylbarbituric acid	N. N. R.	M	0.2
Phanodorn, Cyclobarbital Cyclohexenylethylbarbituric acid	N. N. R.	M	0.1–0.2
Phenobarbital,[b] Phenobarbitone, Luminal Phenylethylbarbituric acid	U. S. P.	P	0.03–0.1
Sandoptal Isobutylallylbarbituric acid	N. N. R.	M	0.2–0.4
Seconal Sodium Sodium allyl(1-methylbutyl)barbiturate	N. N. R.	S	0.1–0.2
Vinbarbital Sodium, Delvinal Sodium Sodium ethyl(1-methyl-1-butenyl)barbiturate	N. N. R.	M	0.1–0.2

[a] Duration of Action: M = Moderate; P = Prolonged; S = Short; VS = Very Short (intravenous).
[b] Sodium salt also in N. N. R. or U. S. P.
[c] Barbital Sodium also known as Medinal.
[d] Thiopental Sodium in U. S. P. XIII.

The medicinal use of the barbiturates is chiefly for the depression of the central nervous system. Depending upon the dose administered and the patient's reaction, the hypnotic effect can vary from a light sleep to a deep coma. The proper oral dose should induce sleep in twenty to sixty minutes. The barbiturates are used to inhibit convulsions as in strychnine poisoning, tetanus, and epilepsy. Phenobarbital is the drug of choice for epileptics because of its selective action upon the motor cortex. Barbiturates

for the excretion of these drugs, especially the more stable compounds, the patient's recovery is delayed. Thiobarbiturates and barbiturates with complex cyclic radicals, e.g., evipal, are less stable and almost completely destroyed in the liver. McNally (3) states that individuals with impaired hepatic function have remained deeply anesthetized for long periods of time from a hypnotic dose of evipal, which in a normal person would have caused an anesthesia for only fifteen minutes. He also states that the longer-

acting barbiturates should not be given to patients with kidney dysfunction, because failure of the kidneys to excrete the barbiturate causes a cumulative toxicity which is noted in cases where this type of drug is used daily. Even in a normal individual a hypnotic dose of a stable barbiturate is detectable in the urine nine days after ingestion of the drug.

McNally warns against the misuse of barbiturates in the field of obstetrics. Gardner recognizes the value of phenobarbital in small doses as a simple sedative, but believes that the barbiturates as a group should be considered hypnotics, and used as such. He fears that many physicians have forgotten that the bromides and small doses of chloral hydrate and chlorobutanol may more efficiently be used as simple sedatives.

The emotional and nervous strain of the unsettled postwar period is making itself apparent by the increase in appeals to the family physician for relief. The barbiturates can be a blessing to individuals undergoing the mental tortures of sleepless nights due to various causes. The layman who experiences this relief and who has not been clearly warned about the possible dangers of intoxication by these drugs will naturally desire to continue using them. The first-time users should have impressed upon them by their physicians the proper use of the barbiturates. The patient's ability to obtain the drug should be curtailed by prescribing small quantities and writing directions for refilling the prescription when necessary. When no specific directions are given these prescriptions should not be refilled.

A vigorous campaign should be instituted by the American Medical Association to educate the physician to his responsibilities in this field of medication before conditions get so bad that public demand will require drastic legislative steps.

Hambourger (4), in 1940 reported that barbiturate addiction accounted for more than 10 per cent of all addiction cases, excluding chronic alcoholism, reported by thirteen hospitals. Two-thirds of the barbiturate addicts who gave information claimed that they became familiar with the drug through a physician. Nearly a third of the addicts for whom the information was recorded developed craving when the barbiturate was withheld. None showed any serious withdrawal symptoms. It is apparent that addiction to barbiturates presents a problem but its seriousness cannot be compared to that caused by narcotics. Even now, after many years of heroic work by Federal agents, the cases of narcotic addiction are far greater than those of barbiturate dependence. The possibility of barbiturate addiction was considered serious enough by the Food and Drug Administration to lead to the ruling which states that the words "may be habit-forming" must appear on all proprietary preparations containing a barbiturate.

Barbiturates were at first thought to be so free from harmful effects that they were prescribed readily in all conditions where drug-induced relaxation or sleep was thought to be desirable. Indeed it is fortunate that with most individuals there is a wide margin between the therapeutic dose and the toxic dose for the barbiturates usually prescribed for oral administration. Ten to fifteen times the therapeutic dose has generally proved fatal although recoveries from massive doses (barbital 150–500 gr., phenobarbital 120–140 gr.) have been reported (4). Nonfatal poisonings from as little as 5 gr. of barbital and 3 gr. of phenobarbital have also been reported. Wide variations in relation to fatal and nonfatal doses have also been noted in hospital records studied by the author. Chronic poisoning is encountered where elimination is slow and cumulative toxic after-effects are manifested in mental and bodily weakness, tremors, and dizziness.

DEATHS FROM BARBITURATES

The increase in deaths caused by barbiturates is evident in the latest figures for the individual states. The available figures from 1936 to 1945, inclusive, are given in Table II. A majority of the states, especially those with large rural populations, show little change in the yearly numbers of deaths caused by barbiturates from 1936 through 1944. Most of the states with large urban populations show increasing numbers of deaths during this period. The

TABLE II.—DEATHS CAUSED BY BARBITURATES: SUICIDAL AND ACCIDENTAL[a]

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945
Alabama[b]	3	10	4	4	3	2	2	..	4	...
Arizona	..	2	6	4	4	3	3	1	3	...
Arkansas[b]	2	1	1	1	2	3	2	2	1	...
California[b]	21	31	29	32	56	63	52	93	108	193
Colorado[b]	..	3	2	4	2	7	8	2	4	...
Connecticut[b]	6	9	9	10	9	8	8	6	10	...
Delaware[b]	1	..	..	..	..	..	..	..	...	...
Dist. of Columbia[b]	4	5	8	8	5	2	2	..	5	...
Florida[b]	8	10	13	10	12	14	5	8	10	...
Georgia[b]	5	8	3	3	3	6	..	4	2	9
Idaho	2	4	2	1	3	1	1	..	1	...
Illinois	33	63	56	51	70	70	24	31	33	60
Indiana[b]	11	18	12	16	27	17	12	9	14	...
Iowa	4	9	15	9	8	14	5	5	8	9
Kansas[c]	3	4	3	9	11	3	3	3	1	9
Kentucky	1	4	6	5	3	4	4	2	3	6
Louisiana[b]	4	1	4	9	2	4	5	1	2	...
Maine[b]	4	3	1	4	3	5	4	..	3	...
Maryland[b]	4	1	1	1	5	3	5	7	7	9
Massachusetts	22	20	20	22	24	35	26	28	22	42
Michigan[b]	11	14	16	26	28	31	13	14	11	...
Minnesota[b]	8	14	11	9	9	12	12	13	14	11
Mississippi[b]	..	3	..	..	9	12	14	6	3	4
Missouri[b]	6	13	16	12	32	7	4	10	11	...
Montana[c]	2	..	..	1	2	1	1	1	4	...
Nebraska[b]	..	2	1	4	6	3	3	2	1	...
Nevada[b]	3	..	1	2	1	..	1	1	...	...
New Hampshire[b]	1	1	4	2	1	9	3	1	...	...
New Jersey[b]	7	4	7	7	17	13	9	12	11	...
New Mexico	1	3	1	2	3	4	..	3	2	...
New York[b]	57	49	62	58	60	65	73	87	98	...
North Carolina[b]	4	2	1	1	5	2	4	4	4	...
North Dakota[c]	1	..	..	..	3	1	2	..	...	...
Ohio	28	21	45	32	55	71	42	38	38	72
Oklahoma[b]	5	6	6	3	1	2	3	4	5	...
Oregon[b]	5	6	5	4	2	6	5	1	4	10
Pennsylvania[b]	12	15	10	15	18	20	18	21	18	...
Rhode Island[b]	1	1	2	1	1	1	1	1	2	...
South Carolina[b]	3	3	3	3	1	2	..	..	3	...
South Dakota	..	..	1	..	..	..	1	1	...	...
Tennessee[b]	4	5	2	4	2	2	3	1	5	...
Texas	7	6	5	8	12	16	7	13	11	...
Utah[c]	2	6	5	3	1	1	1	..	3	...
Vermont[b]	..	1	2	..	3	1	3	..	1	...
Virginia[b]	1	..	..	2	2	3	1	4	7	4
Washington[b]	16	17	10	5	8	9	7	12	11	15
West Virginia[b]	5	3	5	1	5	7	9	4	7	...
Wisconsin	7	12	19	14	15	17	13	9	6	...
Wyoming	..	1	..	..	..	2	..	..	1	...

[a] From U. S. Public Health Service, National Office of Vital Statistics, and State Statistics.
[b] States had enacted laws, as of October 1, 1945, regulating the sale of barbiturates.
[c] States were exercising control of sale of barbiturates by regulation as of October 1, 1945.

available figures for 1945 show tremendous increases in the number of deaths in eight of the fourteen states represented, while only one state shows a definite decrease. The emotion-stirring years of 1939–1941 show the expected high figures, but the deaths in 1945 indicate new all-time highs in many states. The increasing number of deaths caused by barbiturates appears to be about the same for states with and without legal controls for the distribution of barbiturates. It is evident that the control measures in effect today are not succeeding in halting the upward trend in deaths caused by barbiturates.

NONFATAL BARBITURATE POISONINGS

The only reliable source of data on nonfatal poisonings is the hospital record or case history. Data obtained from hospitals by Hambourger for the period 1928 to 1937, inclusive, and by the author for the period 1940 to 1945, inclusive, are recorded in Table III. In the present study more emphasis was placed on obtaining data from enough hospitals in one city (Baltimore) to

make certain that patients from all social and economic levels would be included. The data indicate that the barbiturate danger is prevalent among all classes of the population.

Where data are available from both the 1928–1937 and 1940–1945 periods it will be noted that the percentage ratio of barbiturate poisonings to total admissions has almost doubled, while the percentage ratio of barbiturate poisonings to all drug poisoning cases has increased tremendously. The data from Michael Reese Hospital and Walter Reed General Hospital do not follow the trend with respect to the percentage ratio of barbiturate poisonings to total admissions, but the percentage ratio of barbiturate poisonings to all drug poisonings remained the same in the first hospital while the figure of 42.9 per cent for the second hospital shows that almost half its poisoning cases were caused by barbiturates. The data from Johns Hopkins Hospital show that the percentage ratio of barbiturate poisonings to total poisonings for the 1940–1945 period is lower than for the 1936–1937 period. A yearly breakdown shows that this ratio increased each year from a low of 0.5 per cent in 1940 to a high of 21.2 per cent in 1945.

Applying the percentage ratios of barbiturate poisonings to total admissions obtained for the 1940–1945 period (excluding Boston City Hospital) to the same number of admissions for each corresponding hospital as reported in the earlier survey, we obtain the following figures: total admissions 786,766; barbiturate poisonings for earlier period 182; barbiturate poisonings for later period 339. This gives a composite percentage ratio of 0.023 for the 1928–1937 period as compared with a composite percentage ratio of 0.043 for the 1940–1945 period, or an increase of over 86 per cent in the number of barbiturate poisoning cases. In the case of

TABLE III.—ACUTE POISONING BY BARBITURATES

Hospital	1928–1937, Inclusive					1940–1945, Inclusive				
	Hospital Admissions, All Causes (A)	Poisoning Cases Except CO and and Alc. (P)	Barbiturate Poisoning (B)	Percentage of All Poisoning Cases, $\frac{B}{P}$ 100	Percentage of All Admissions, $\frac{B}{A}$ 100	Hospital Admissions, All Causes (A)	Poisoning Cases Except CO and Alc. (P)	Barbiturate Poisoning (B)	Percentage of All Poisoning Cases, $\frac{B}{P}$ 100	Percentage of All Admissions, $\frac{B}{A}$ 100
Boston City	331,481	2214	391	17.7	0.118	163,469[a]	950	271	28.5	0.166
Peter Bent Brigham, Boston	43,885	214	26	12.1	0.059	.....	...	...	..	...
Cleveland City	129,983	..	60	..	0.046	74,709	311	92	29.6	0.123
University Clinics, Chicago	63,076[b]	117	18	15.4	0.028	40,339	55	15	27.3	0.037
University Hospitals, Cleveland	91,703	245	23	9.4	0.025	.....	...	...	..	...
St. Mary's, St. Louis	75,024	99	18	18.2	0.024	52,516	110	18	16.4	0.034
Michael Reese, Chicago	142,067	169	34	20.1	0.024	102,026	40	8	20.0	0.008
Presbyterian, New York	135,352	444	22	5.0	0.016	139,499	193	45	23.3	0.032
Johns Hopkins, Baltimore	32,703[c]	27	5	18.5	0.015	118,407	824	27	3.3	0.023
Baylor University, Dallas, Texas	109,138	293	15	5.1	0.014	111,533	103	50	48.5	0.045
Baltimore City	25,356[d]	114	3	2.6	0.012	37,191	235	19	8.1	0.051
Walter Reed General, Washington, D. C.	74,067	..	7	..	0.009	35,755[e]	7	3	42.9	0.008
Union Memorial, Baltimore	.....	..	...	..	...	32,665	90	29	32.2	0.089
University Hospital, Baltimore	.....	..	...	..	...	69,287	123	22	17.9	0.032
Sinai, Baltimore	.....	..	...	..	...	39,331	110	12	10.9	0.031
Mercy Hospital	.....	..	...	..	...	43,548	77	8	10.3	0.018

[a] 1940–1943, inclusive.
[b] 1927–1938, inclusive.
[c] 1936–1937, only.
[d] 1935–1937, inclusive.
[e] 1943–1944 only.

Boston City Hospital for which we have data through 1943 only, the percentage ratio of 0.118 for the 1928–1937 period compared with that of 0.166 for the 1940–1943 period shows a 41 per cent increase in the frequency of occurrence of barbiturate poisoning cases.

Applying the percentage ratios of barbiturate poisonings to all drug poisoning cases (except alcohol and carbon monoxide) obtained for the 1940–1945 period (excluding Boston City Hospital) to the same number of total drug poisoning cases for each corresponding hospital as reported in the earlier survey, we obtain the following figures: total drug poisoning cases 1263; barbiturate poisonings for earlier period 115; barbiturate poisonings for later period 337. This gives a composite percentage ratio of 9.1 for the 1928–1937 period as compared with 26.7 for the 1940–1945 period, or an increase of over 193 per cent in the frequency of barbiturate poisonings compared to all drug poisonings. Boston City Hospital shows a percentage ratio of 17.7 for the 1928–1937 period compared with that of 28.5 for the 1940–1943 period, or a 61 per cent increase in the frequency of occurrence of barbiturate poisoning cases.

The hospital data for the 1928–1937 period show that in ten hospitals with total admissions of 1,049,785, barbiturates were responsible for one-seventh of the acute poisonings due to all drugs except alcohol and carbon monoxide. The present survey shows that in fourteen hospitals with total admissions of 1,060,275, barbiturates were responsible for one-fifth of the acute poisonings due to all drugs except alcohol and carbon monoxide.

The conditions existing in the period up to 1937 were responsible for the introduction of a resolution at the June, 1937 meeting of the American Medical Association on the "Evils from Promiscuous Use of Barbituric Acid and Derivative Drugs." The resolution included the following statement: "The evils of these drugs include habit formations, toxic cumulative action, their substitution for alcoholic beverages for drunken episodes, their use for successful as well as unsuccessful suicidal attempts, their improper use being a recognized causative factor in many motor accidents and their improper use being a recognized etiologic factor in some criminal assaults . . . ." If the conditions responsible for the position taken by the A. M. A. in 1937 are reflected in the hospital survey made by Doctor Hambourger at the invitation of the A. M. A. Council on Pharmacy and Chemistry, then certainly a much more alarming condition is indicated by the present study.

Data obtained from the publications of the United States Department of Commerce, Bureau of the Census, indicate that while the trend for the United States is lower in suicides and fatal poisonings by all solid and liquid poisons, suicides and fatal poisonings by barbiturates are increasing. This is shown in Figures 1 and 2.

These data emphasize the increase in the number of barbiturate poisonings. About the middle of 1945 the Chief Medical Examiner of New York City reported an increase in the number of deaths in the city from consumption of sleeping tablets from a normal (?) of 40 per year to 47 in the last three months. Early in 1946 the New York City hospitals were reporting a death caused by barbiturates every thirty-six hours. Is there any wonder that New York City already has enacted more stringent legislation for the control of these drugs? The use of barbiturates in the United States has increased at such a rate that whereas in 1936 two hundred and thirty thousand pounds were produced, in 1945 the production of barbiturates was five hundred and fifty thousand pounds.

Many lay "pharmacologists" have discovered that if barbiturates are taken with alcohol they can obtain effects ranging from a "cheap drunk" to a "heroin reaction." In the New York Harlem section the effect is called "Wild Geronimo." These people refer to the barbiturates as goof pills, yellow jackets, red dogs, or red birds, depending upon the color of the capsules, and the combination with beer or liquor is called "a bolt and a jolt."

The use of barbiturates by criminals is considered to be of secondary concern since these people make up a small fraction of the population. Of greater concern are the thou-

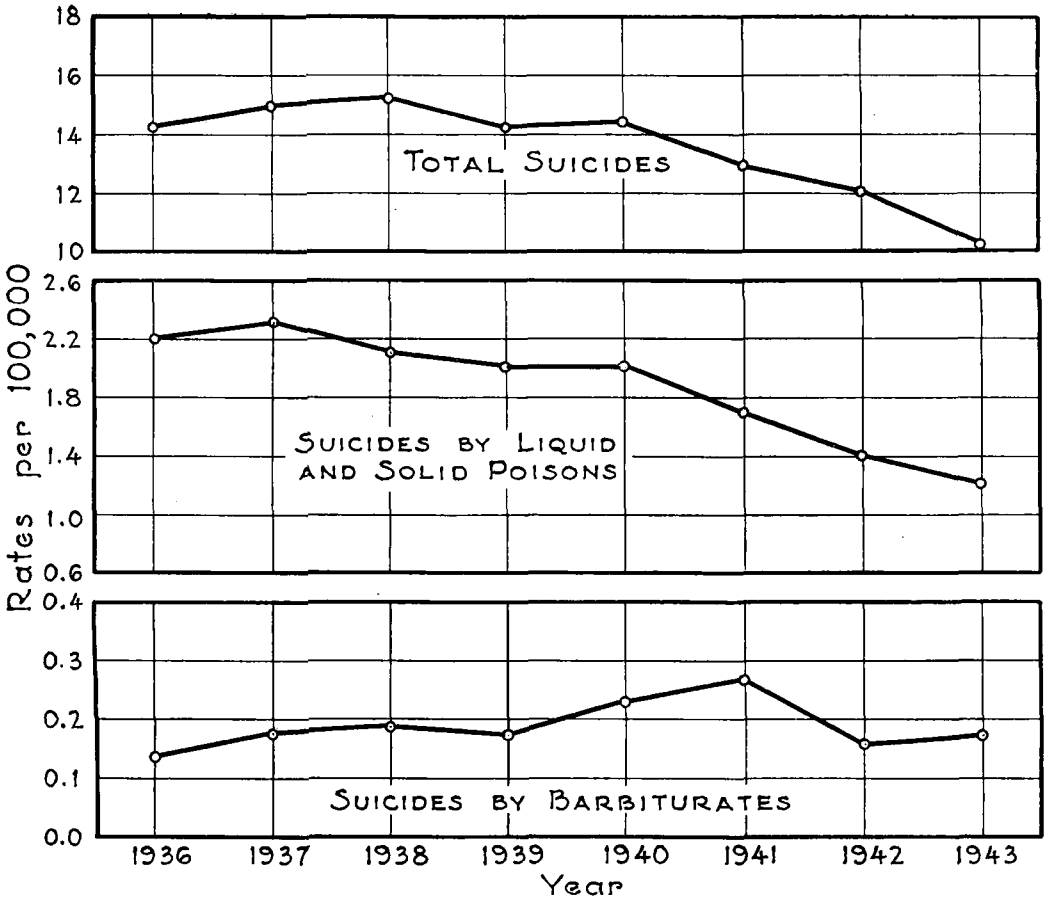

Fig. 1.—Suicides—United States (Bureau of Census Data)

sands of people who regard these compounds as harmless and gradually use them to excess. What is becoming the classic example was discovered not long ago in Waco, Texas. A kindergarten teacher noticed the unusual behavior of a pair of twins. She found that one of them had a box of pills which the child said her father had given to her. Investigation showed that the father, a factory worker, had been put on the night shift. Unable to adjust himself to the new hours he became addicted to sleeping pills. He was still disturbed by the noise of the twins playing, so he started giving them pills too. The children were taking them regularly. This story will be retold many times before adequate control of barbiturates is finally established.

Many accidental cases of barbiturate intoxication are discovered and treated before death takes its toll. Frequently these individuals tell of having taken the usual dose of the drug which did not bring sleep. Then, in the mentally befuddled state induced by the barbiturate, they took more of the drug. How much more they did not know. Barbiturates have now achieved the questionable honor of being chosen as the chemical instrument of suicide, second only to carbon monoxide.

Where can people get more barbiturates than they should have? From physicians; from pharmacists (with prescriptions, and in some cases without prescriptions); from some nurses; from wholesale drug houses; from jobbers; and from individuals who "know the ropes." A strong campaign to educate all physicians, pharmacists, and nurses to the dangers of these drugs should be initiated immediately by the American Medical Association and the AMERICAN PHARMACEUTICAL ASSOCIATION. The public should be made aware of the dangers accompanying misuse of the barbiturates

Prominent newspaper ballyhoo everytime a famous or notorious individual succumbs to sleeping pills should not dramatize the ease with which the victim passed away.

I believe, that if all the unfortunate cases of barbiturate addiction and intoxication due to barbiturates obtained from physicians and pharmacists could be eliminated, the tragic picture presented today would be only

groups have responded as they have in the past and are conscientiously striving to aid in the formulation of legal safeguards to keep the growing monster under control.

Pharmacists should not depend entirely upon those seemingly untiring giants in the field of pharmaceutical advancement Dr. Robert P. Fischelis, Dr. R. L. Swain, and the other members of the group working on

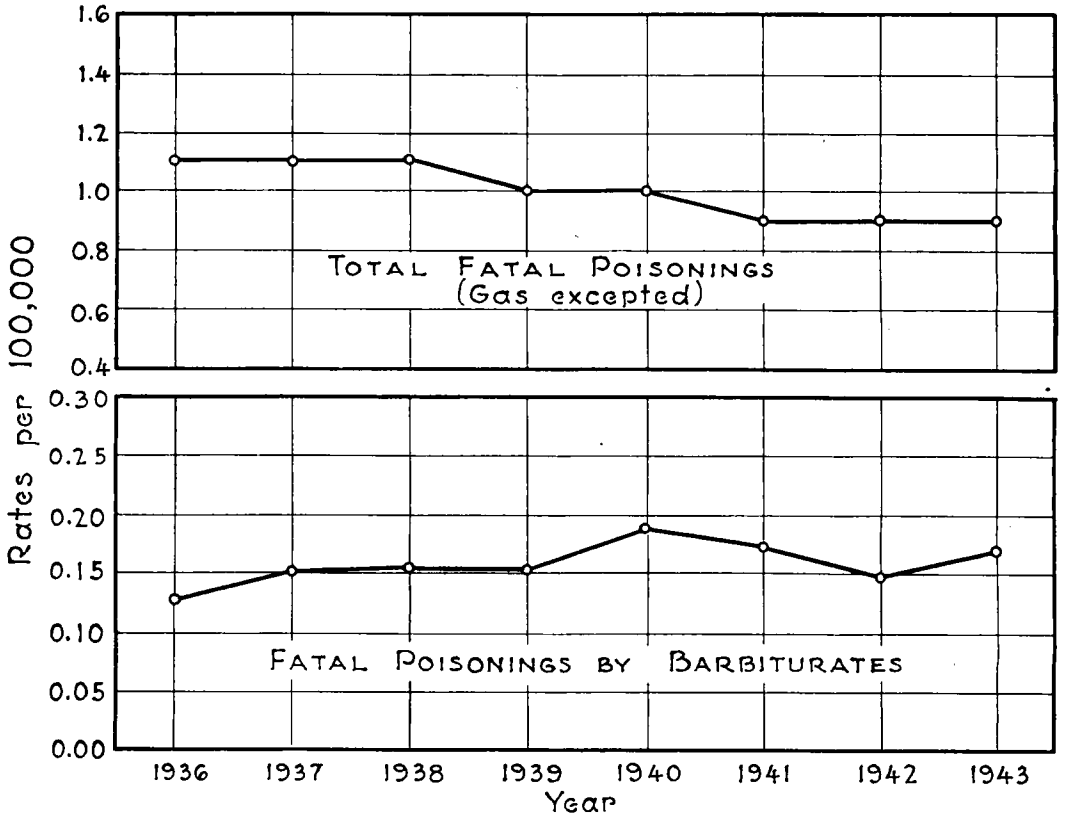

Fig. 2.—Fatal Poisonings—United States (Bureau of CensusDate)

very slightly bettered. Without the knowledge or intent of most manufacturers, wholesalers, dealers, and jobbers, most of the barbiturates that are illegitimately and harmfully used get into the hands of the users through nonprofessional channels.

BARBITURATE CONTROL NEEDED

There can be no doubt that uncontrolled traffic in barbiturates is a growing menace to the public health. Responsible authorities have pointed with alarm and have called for rigid controls of this group of drugs. The leaders of the medical and pharmaceutical

uniform laws affecting pharmacy and medicine. They cannot be expected to achieve results without the active aid and cooperation of the rank and file of the organizations they represent. When A. L. I. Winne of the A. PH. A. Committee on Legislation presented a plan for a uniform state law for the control of barbiturates to the House of Delegates of the AMERICAN PHARMACEUTICAL ASSOCIATION, the most that could be accomplished at that time was a recorded agreement in principle to a uniform state law. More concrete results must be achieved soon or the interested public health groups will find

that they are fighting a losing battle against complete government control. The American Medical Association is now in a position where they are fighting to preserve as much professional freedom as possible in the face of the pressure by certain groups to push through the Congress the modified Wagner–Murray–Dingell bills (S. 1606-H.R. 4730). They still tend to dismiss possible Federal control of barbiturates by saying that the government authorities are not inclined to include barbiturates under the Federal narcotic act. Indeed, Dr. Paul Dunbar, U. S. Commissioner of Foods and Drugs, in discussing Federal control over the distribution of barbiturates and other sleep-producing drugs, stated, "A Federal law would be too complicated and drastic. Uniform state laws would be more satisfactory" (5). Dr. Dunbar's opinion does not mean that a Federal statute regulating barbiturates cannot be passed. Not all Federal and state enforcement officers agree with Dr. Dunbar. A bill (H.R. 6178) was introduced in the Seventy-Ninth Congress by Representative Edith Rogers of Massachusetts that would designate barbiturates as narcotic drugs and place them under all the provisions now effective for the handling of narcotics. This is the first attempt. It will not be the last. It is not surprising that a congressional representative from Massachusetts should be sufficiently interested to do something about the barbiturate situation. Table II reveals that the total deaths caused by barbiturates in Massachusetts in 1945 are 91 per cent higher than the number occurring in 1944. Table III shows that the Boston City Hospital, which has a very large number of admissions, had the highest percentage ratio of barbiturate poisonings to total admissions of any of the listed hospitals. However, it is surprising that the lady's home state, as of October 1, 1945, had not enacted legislation seeking to control barbiturate distribution. Nevertheless, the fact remains that the conditions that have created the demand for such legislation are not improving, as a glance at the data clearly shows.

If physicians and pharmacists would avoid Federal control let them get together on uniform state legislation and do it quickly. Dr. Fischelis' comprehensive review and analysis of the laws pertaining to the control of the distribution of barbiturates, in force in thirty-two states, two possessions, and the District of Columbia as of October 1, 1945, appeared recently (6). This clear picture of the present laws should lend itself to the framing of effective legislation for the control of barbiturate manufacture and distribution. Dr. Fischelis and the members of the A. PH. A. Committee on Legislation have done their part. The points of greatest disagreement as to the wording of a uniform state law seem to center around the renewals of prescriptions and the question of record keeping. Why not utilize the splendid efforts of the AMERICAN PHARMACEUTICAL ASSOCIATION Committee on Legislation up to that point? The individual states can phrase the controversial sections as they see fit. There is no doubt that the phraseology applying to the manufacture and distribution of barbiturates until they reach the physician and pharmacist should be similar in all states. If this cannot be done it might as well be turned over to the Federal authorities.

The problem is here and it is growing. Something must be done to solve it and we should do it as soon as possible.

SUMMARY

1. The development and therapeutic status of the barbituric acid derivatives are reviewed. The accepted clinically valuable barbiturates are tabulated.

2. Deaths caused by barbiturates are shown to be increasing in many states, especially in those states with large urban populations. Where figures for 1945 are available, a sharp increase is indicated for many states. The state laws affecting the distribution of barbiturates that had been passed as of October 1, 1945 appear to have had little effect on the increase in mortality due to barbiturates.

3. The percentage ratio of cases of barbiturate poisonings to total admissions in the same hospitals for the 1928–1937 and 1940–1945 periods show an 86 per cent increase in the frequency of occurrence of barbiturate poisonings in the 1940–1945 period.

4. The percentage ratio of barbiturate poisonings to all drug poisonings (carbon monoxide and alcohol excepted) in the same hospitals for the 1928–1937 and 1940–1945 periods show a 193 per cent increase in the frequency of occurrence of barbiturate poisonings in the 1940–1945 period.

5. Barbiturates accounted for one-seventh of the total drug poisoning cases in ten hospitals with total admissions of 1,049,785 during 1928–1937. Barbiturates accounted for one-fifth of the drug poisoning cases in fourteen hospitals with total admissions of 1,060,275 during 1940–1945.

6. Available data for the United States show that while the yearly cases of suicides and fatal poisonings by all solid and liquid poisons indicate a downward trend, the yearly cases of suicides and fatal poisonings by barbiturates are increasing.

7. The growing nature of the problem is discussed and the urgent need for corrective uniform state legislation is stressed.

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Additional information was obtained from Statisticians at various State Health Departments, from Hospital Officials and Statisticians, and by personal examination of records and case histories in Baltimore City hospitals.

Biologic Assay of Mercury Ointments*,†

By EDWIN P. LAUG, ELIZABETH A. VOS, and FRIEDA M. KUNZE

Using the storage of mercury in the kidney of the rat as a measure of cutaneous penetration, 8 official mercury ointments have been assayed. Mercury oleate and nitrate ointments showed the greatest penetration; calomel and yellow mercuric oxide showed the least. Intermediate in penetration were mercurial, ammoniated and red oxide of mercury ointments. The degree of penetration of mercury was relatively insensitive to large differences in concentration of mercury in the ointments.

REFERENCE to the U. S. P. XII and the N. F. VII reveals that there are 8 different official mercury ointments. The acceptability of these ointments has been judged largely on the basis of either physical properties or the degree of their therapeutic effect. To date, no information has been forthcoming concerning the relative efficiency with which mercury penetrates the skin from these ointments. Recently the authors developed a method (1, 2) for the assay of different types of calomel ointments which was based on the ability of the mercury to penetrate the skin. This method has been applied to the 8 above-mentioned mercury ointments, but with the tacit assumption that skin permeability to mercury is not necessarily the sole criterion of therapeutic efficiency.

EXPERIMENTAL

Method.—The principle of this method is based on the observation that the concentration of mercury in the kidney is a measure of the amount which has penetrated the skin (1). Briefly, the assay is carried out as follows: Rats are lightly anesthetized, and 0.4 Gm. of mercury ointment is inuncted over an area of 29 $(cm.)^2$ ($1^1/_2 \times 3$ in.) of the clipped dorsal skin. Inunction is made for two minutes with a glass rod. Then, without removal of the excess ointment, the animal is wrapped in a cylindrical celluloid shield cemented to the body at the shoulders and hips. The shield is sufficiently stiff so that the animal is confined after the fashion of a straight jacket, and is thus prevented from

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